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10/692,764	10/24/2003	Stuart B. Levy	PAZ-205CP	8952

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EXAMINER	
MAKAR, KIMBERLY A	
ART UNIT	PAPER NUMBER
1636	
MAIL DATE	DELIVERY MODE
03/04/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/692,764	LEVY ET AL.	
	Examiner	Art Unit	
	Kimberly A. Makar, Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 November 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,37-47,54 and 57-64* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1, 37-47, 54 and 57-64* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 October 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

1. The amendments filed on 11/05/07 are acknowledged. Applicants have cancelled claims 2-6, 8, 10-11. Applicants have added new claims 58-64. Thus currently, claims 1, 37-47, 54 and 57-64 are pending and under examination. In the previous office action the following rejections were made:

- Claims 1,8, 11,36-47 were rejected on the ground of nonstatutory obviousness- type double patenting as being unpatentable over claims in EACH of U.S. Patent Nos. 6,500,812, 6,624,168, 6,642,270, 6,683,068, 6,818,634, 6,818,635, 6,833,365, 6,846,939, 6,849,615,7,045,507, and 7,094,806.

- Claims 1, 8, 11, 36-47 were provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims of copending Application Nos. 10/692,563, 10/752,378, 10/786,881, 10/943,571.

- Claims 1-6, 8, 10, 11, 36-47, 54, and 57 were rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement.

- Claims 1-6, 8, 10, 11, 36-47, 54, and 57 were rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

- Claims 1, 2, 8, 10, 11, 36-38 were rejected under 35 U.S.C. 102(b) as being taught by Yrjanheikki et al (Tetracyclines Inhibit Microglial Activation and are Neuroprotective in Global Brain Ischemia. PNAS, 1998.95:15769-15574).

- Claims 1, 8, 11, 36-47 were rejected under 35 U.S.C. 102(e) as being anticipated by Nelson et al (US Patent No. 6,500,812).

- Claims 1, 8, 11, 36-47 were rejected under 35 U.S.C. 102(e) as being anticipated by Nelson et al (US Patent No. 6,624,168).

- Claims 1, 8, 11, 36-47 were rejected under 35 U.S.C. 102(e) as being anticipated by Nelson et al (US Patent No. 6,642,270).

- Claims 1, 8, 11, 36-47 were rejected under 35 U.S.C. 102(e) as being anticipated by Nelson et al (US Patent No. 6,683,068).

- Claims 1, 8, 11, 36-47 were rejected under 35 U.S.C. 102(e) as being anticipated by Nelson et al (US Patent No. 6,818,634).

- Claims 1, 8, 11, 36-47 were rejected under 35 U.S.C. 102(e) as being anticipated by Nelson et al (US Patent No. 6,818,635).

- Claims 1, 8, 11, 36-47 were rejected under 35 U.S.C. 102(e) as being anticipated by Nelson et al (US Patent No. 6,846,939).

- Claims 1, 8, 11, 36-47 were rejected under 35 U.S.C. 102(e) as being anticipated by Nelson et al (US Patent No. 6,849,615).

- Claims 1, 8, 11, 36-47 were rejected under 35 U.S.C. 102(e) as being anticipated by Draper et al (US Patent No. 7,045,507).

- Claims 1, 8, 11, 36-47 were rejected under 35 U.S.C. 102(e) as being anticipated by Nelson et al (US Patent No. 7,094,806).

- Claims 1, 8, 11, 36-47 were rejected under 35 U.S.C. 102(e) as being anticipated by Nelson et al (US Patent No. 7,202,235).

- Claims 1, 8, 11, 36-47 were rejected under 35 U.S.C. 102(e) as being anticipated by Draper et al (US Patent Publication No. US 20040242548).

- Claims 1, 8, 11, 36-47 were rejected under 35 U.S.C. 102(e) as being anticipated by Huss et al (US Patent Publication No. US 20040266740).

- Claims 1, 8, 11, 36-47 were rejected under 35 U.S.C. 102(e) as being anticipated by Nelson et al (US Patent Publication No. US 20050026876).

- Claims 1, 8, 11, 36-47 were rejected under 35 U.S.C. 102(e) as being anticipated by Draper et al (US Patent Publication No. US 20050070510).

2. Any rejection not maintained in this office action is withdrawn.

3. The following rejections were necessitated by applicant's amendments.

Applicants have amended the claims to recite a method for treating a DTMR

"associated with splicing" which was not a limitation in any previously presented claims.

Double Patenting

4. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

5. Claims 1, and 37-47 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims in EACH of U.S. Patent Nos. 6,500,812, 6,624,168, 6,642,270, 6,683,068, 6,818,634, 6,818,635, 6,846,939, 6,849,615, 7,045,507, and 7,094,806. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims represent a genus over claims in EACH of U.S. Patent Nos. 6,500,812, 6,624,168, 6,642,270, 6,683,068, 6,818,634, 6,818,635, 6,846,939, 6,849,615, 7,045,507, and 7,094,806.

6. The instant claims recite "A method for treating a subject for a DTMR *associated with splicing*, comprising: administering to said subject an effective amount of a tetracycline compound, such that said DTMR is treated." Thus, this method recites the

single step of administering an effective amount of a tetracycline compound to a subject. The instant specification teaches no specific definition of DTMR (Disorders Treatable by Modulation of RNA), but recites a DTMR associated with splicing include:

7. Other exemplary DTMRs include disorders caused by, or associated with splicing. For example, some disorders associated with defects in pre-mRNA processing result from a loss of function due to mutations in regulatory elements of a gene. Examples of such mutations are described in Krawczak et al. (1992) Hum. Genet, 90:41- 54; and Nakai et al. (1994) Gene 14:171-177. Other DTMR include disorders which have been attributed to a change in trans-acting factors. Examples of DTMRs which are associated with splicing include those described in Philips et al. (2000), Cell. Mol. Life Sci., 57:235-249), as well as, FTDP- 17 (frontotemporal dementia with parkinsonism) and/β-thalassemia.
8. Certain DTMRs associated with splicing include those which are generated by point mutations that either destroy splice-sites or generate new cryptic sites in the vicinity of normally used exons. Examples of such DTMRs include cystic fibrosis (Friedman et al. (1999) Jr. Biol. Chem. 274:36193-36199), muscular dystrophy (Wilton et al. (1999) Neuromuscul. Disord. 9:330-338), and eosinophilic diseases (Karras et al., (2000) Mol. Pharamcol. 58:380-387).
9. Other DTMRs include cancers which may change splicing patterns during cancer formation and progression. Example of such cancers include, but are not limited to leukemia, colon/rectal cancer, myeloid leukemia, breast cancer; gastric carcinomas, acute leukemia, multiple myeloma, myeloid cell leukemia, lung cancer, prostate cancer, etc. Addition DTMRs associated with splicing are discussed in Stoss et al., (2000), Gene Ther. Mol. Biol. 5:9-30). (page 9, lines 8-29).

10. U.S. Patent Nos. 6,500,812 (claims 14 and 15) which teaches that one tetracycline compound responsive state includes cancer (column 16, lines 30-36), 6,624,168 (claims 6-11) which teaches that one tetracycline compound responsive state includes cancer (column 12, lines 9-14), 6,642,270 (claims 6-14) which teaches that one tetracycline compound responsive state includes cancer (column 12, lines 1-3), 6,683,068 (claims 17-21) which teaches that one tetracycline compound responsive state includes cancer (column 24, lines 7-11), 6,818,634 (claims 27-29) which teaches that one tetracycline compound responsive state includes cancer (column 26, lines 47-

53), 6,818,635 (claims 23-26) which teaches that one tetracycline compound responsive state includes cancer (column 42, lines 59-65), 6,846,939 (claims 21-24) which teaches that one tetracycline compound responsive state includes cancer (column 25, lines 27-32), 6,849,615, (claims 6-10) which teaches that one tetracycline compound responsive state includes cancer (column 16, lines 1-6), 7,045,507 (claims 1-14, 22-55, 62-65, and 75) which teaches that one tetracycline compound responsive state includes cancer patient (column 56, lines 1-5), and 7,094,806 (claims 7-11) which teaches that one tetracycline compound responsive state includes cancer (column 12, lines 36-41) recite methods of treating a subject with bacterial, fungal or tetracycline responsive states, an effective amount of tetracycline compounds and their derivatives. These methods teach the treatment of mammals, including humans. The instant claims 1, and 36-47 recite methods of treating a DTMR associated with splicing with the single step of administering an effective amount of a tetracycline compound; the disclosed definition of a DTMR encompasses the species diseases and disorders disclosed in the patents. Therefore, a method of treating a DTMR associated with splicing (including cancer as taught by applicant above) would include a method of treating a bacterial infection, a fungal infection, or a tetracycline response state associated with cancer using an effective amount of tetracyclines.

11. The claims in each patent are more narrowly drawn (representing the species) than the corresponding instant genus claims. Thus, the invention of the instant claims 1, 36-47 are not patentably distinct from those of respective patented claims.

12. Claims 1, 36-47 are directed to an invention not patentably distinct from claims of commonly assigned US patents 6,500,812, 6,624,168, 6,642,270, 6,683,068, 6,818,634, 6,818,635, 6,846,939, 6,849,615, 7,045,507, and 7,094,806. Specifically, the claims in each patent are more narrowly drawn (representing the species) than the corresponding instant genus claims.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP Chapter 2300). Commonly assigned 6,500,812, 6,624,168, 6,642,270, 6,683,068, 6,818,634, 6,818,635, 6,846,939, 6,849,615, 7,045,507, and 7,094,806, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications pending on or after December 10, 2004.

Response to Arguments

13. Applicant's arguments filed 11/05/07 have been fully considered but they are not fully persuasive. Applicant's traverse the rejection of Claims 1, 8, 11,36-47 on the ground of nonstatutory obviousness- type double patenting as being unpatentable over claims in EACH of U.S. Patent Nos. 6,500,812, 6,624,168, 6,642,270, 6,683,068, 6,818,634, 6,818,635, 6,833,365, 6,846,939, 6,849,615, 7,045,507, 7,094,806 and 7,202,235. Applicants argue that none of the aforementioned patent read on a DTMR associated with splicing. The examiner is respectfully not fully persuaded. The instant specification fails to define a "DTMR associated with splicing" however, applicants do provide examples that read on a "DTMR associated with splicing" to include cancers. Of the US Patents 6,500,812, 6,624,168, 6,642,270, 6,683,068, 6,818,634, 6,818,635, 6,833,365, 6,846,939, 6,849,615, 7,045,507, and 7,094,806, *only 6,833,365 and 7,094,804 do not specifically teach that one of the disorders capable of being treated with a tetracycline derivative is cancer*. Specifically, US Patents 6,500,812, 6,624,168, 6,642,270, 6,683,068, 6,818,634, 6,818,635, 6,846,939, 6,849,615, and 7,045,507 and 7,094806 all specifically teach that cancer is one disease that can be treated using a tetracycline derivative of the invention. ***Thus, the obvious type double patenting rejection over claims 1, 36-47 is maintained over US Patents US 6,500,812, US 6,624,168, US 6,642,270, US 6,683,068, US 6,818,634, US 6,818,635, US 6,846,939, US 6,849,615, US 7,045,507 and US 7,094,806. However, the obvious type double patenting rejection over US Patents 6,833,365 and 7,202,235 is withdrawn.***

14. Claims 1, 36-47 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims of copending Application Nos. 10/692,563, 10/752,378, 10/786,881, 10943,571. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims represent a genus over claims in EACH of copending Application Nos. 10/692,563, 10/752,378, 10/786,881, 10/943,571.

15. The instant claims recite "A method for treating a subject for a DTMR associated with splicing, comprising: administering to said subject an effective amount of a tetracycline compound, such that said DTMR is treated." Thus, this method recites the single step of administering an effective amount of a tetracycline compound to a subject. A DTMR reads on bacterial infections (citrus greening disease), viral infections (HIV), diseases, cancers, and fungal infections (pneumonitis) (see above).

16. Copending Application Nos. 10/692,563, 10/752,378, 10/786,881, 10/943,571 recite methods of treating Malaria, a tetracycline responsive state, bacterial infections and killing a fungus comprising the administration of an effective amount of a tetracycline compound. The instant claims 1, 8, 11, 36-47 recite methods of treating a DTMR by administering an effective amount of a tetracycline compound; the disclosed definition of a DTMR encompass the species diseases and disorders disclosed in the patent applications. Therefore, a method of treating a DTMR would include a method of treating a bacterial infection, a fungal infection, or a tetracycline response using an effective amount of tetracyclines.

17. The claims in each application are more narrowly drawn (representing the species) than the corresponding instant genus claims. Thus, the invention of the instant claims 1, 36-47 are not patentably distinct from those of respective application claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1, 36-47 are directed to an invention not patentably distinct from claims of commonly assigned US patent applications 10/692,563, 10/752,378, 10/786,881, 10/943,571. Specifically, the claims in each patent application are more narrowly drawn (representing the species) than the corresponding instant genus claims.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP Chapter 2300). Commonly assigned copending applications 10/692,563, 10/752,378, 10/786,881, 10/943,571, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

18. A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon

the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications pending on or after December 10, 2004.

Response to Arguments

19. Applicant's arguments filed 11/05/07 have been fully considered but they are not persuasive. Applicants argue that they will consider submitting terminal disclaimers if appropriate. The examiner is respectfully not persuaded, and the provisional rejection over claims 1, 36-47 is maintained.

Claim Rejections - 35 USC § 112

20. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

21. Claims 1, 36-47, 54, 57-64 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The instant claims are drawn to a method of treating any Disease Treatable by Modulation of RNA (DMTR) ***associated with splicing*** comprising the administration of a tetracycline derivative compound to a subject in an effective amount to modulate splicing. The method involves the modulation of subject's RNA splicing of

mRNA. The method reads on treating humans. ***This rejection is modified to address amendments to claims.***

22. The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the specification coupled with information known in the art without undue experimentation (*United States v. Telectronics*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is needed is not based on a single factor but rather is a conclusion reached by weighing many factors. These factors were outlined in *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter., 1986) and again in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988) and include the following:

23. *1) The nature of the invention.* The invention involves a method of treating *any* Disease Treatable by Modulation of RNA (DMTR) associated with splicing comprising the administration of *any* tetracycline derivative compound to *any* subject in an effective amount. The method involves the modulation of subject's RNA splicing of mRNA in the subject, including activation of cryptic splice sites, silencing of splice sites, silencing of exonic or intronic splicing enhancers, silencing of exonic or intronic splicing silencers, the alteration of the binding or component of the splicing machinery to the RNA, or affecting the intermolecular interactions between components of the splicing machinery. Furthermore, the method reads on treating humans.

24. *2) Number of working examples*. Applicants have provided multiple examples of making different tetracycline derivate compounds (see examples 1-2). Applicant's have

provided a single example of the treatment of two independent murine macrophage cells lines (J774.2 and RAW 264.7) in which there is up-regulation or down regulation of mRNA as assed by microarray technology (see example 3). There is no disclosure if these murine macrophage cells are an art accepted model for a particular DMTR associated with splicing. Example 4 investigates the *in vitro* cytotoxicity of two tetracycline compound derivatives (minocycline and doxycycline) on Cos-1 and CHO-K1 cells and Example 5 investigates the *in vitro* anti-bacterial activity of 2 undisclosed tetracycline derivative compounds. There is no disclosure of an *in vivo* treatment of a particular DMTR associated with splicing in a working example. There is no disclosure in Example 3 of how the modulation of RNA occurs (translation, half-life, translocation, protein binding, or splicing) is effected by the exposure to the tetracycline derivatives. Applicant's do not disclose which particular genes are up-regulated or down regulated, but simply disclose the total up-regulated or down-regulated genes in table 3 (page 116 of the instant specification). There is no disclosure if the modulation of RNA splicing results in any protein modulation.

25. *3) Amount of direction or guidance present.* The applicants provide very generic teaching of methods of treating a subject for a DTMR. The specification teaches that a DTMR associated with splicing includes:

26. Other exemplary DTMRs include disorders caused by, or associated with splicing. For example, some disorders associated with defects in pre-mRNA processing result from a loss of function due to mutations in regulatory elements of a gene. Examples of such mutations are described in Krawczak et al. (1992) Hum. Genet, 90:41- 54; and Nakai et al. (1994) Gene 14:171-177. Other DTMR include disorders which have been attributed to a change in trans-acting factors. Examples of DTMRs which are associated with splicing include those described in Philips et al. (2000), Cell.

Mol. Life Sci., 57:235-249), as well as, FTDP- 17 (frontotemporal dementia with parkinsonism) and/β-thalassemia.
27. Certain DTMRs associated with splicing include those which are generated by point mutations that either destroy splice-sites or generate new cryptic sites in the vicinity of normally used exons. Examples of such DTMRs include cystic fibrosis (Friedman et al. (1999) Jr. Biol. Chem. 274:36193-36199), muscular dystrophy (Wilton et al. (1999) Neuromuscul. Disord. 9:330-338), and eosinophilic diseases (Karras et al., (2000) Mol. Pharamcol. 58:380-387).
28. Other DTMRs include cancers which may change splicing patterns during cancer formation and progression. Example of such cancers include, but are not limited to leukemia, colon/rectal cancer, myeloid leukemia, breast cancer; gastric carcinomas, acute leukemia, multiple myeloma, myeloid cell leukemia, lung cancer, prostate cancer, etc. Addition DTMRs associated with splicing are discussed in Stoss et al., (2000), Gene Ther. Mol. Biol. 5:9-30). (page 9, lines 8-29).
29.

30. Applicant's single method step includes the "administering to said subject an effective amount of a tetracycline compound" but does not disclose how the single application of the tetracycline would differ from treating "β-thalassemia" to "prostate cancer", other than to change the effective amount and the applications. Applicants do teach that the tetracycline compounds can be co-administered with a second agent "the second agent can be any agent which is known in the art to treat, prevent, or reduce the symptoms of a DTMR" including chemotherapeutic agents (page 93). Applicant further teach that the tetracycline compound can be administered as a pharmaceutical composition with a myriad of carriers, and methods of administration (page 94-9100). Applicants contend that the "effective amount" simply depends on size and weight of the subject, but then teaches that the choice of tetracycline compound can affect the "effective amount". Applicant's teaches, "[o]ne of ordinary skill in the art would be able to study the aforementioned factors and make the determination regarding the effective amount of the tetracycline compound without undue experimentation."

Applicant's further teach how actual dosages are determined by experimentation by the skilled artisan:

Actual dosage levels of the active ingredients in the pharmaceutical compositions of this invention may be varied so as to obtain an amount of the active ingredient which is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being toxic to the patient.
The selected dosage level will depend upon a variety of factors including the activity of the particular compound of the present invention employed, or the ester, salt or amide thereof, the route of administration, the time of administration, the rate of excretion of the particular compound being employed, the duration of the treatment, other drugs, compounds and/or materials used in combination with the particular compound employed, the age, sex, weight, condition, general health and prior medical history of the patient being treated, and like factors well known in the medical arts.

A physician or veterinarian having ordinary skill in the art can readily determine and prescribe the effective amount of the pharmaceutical composition required. For, example, the physician or veterinarian could start doses of the compounds of the invention employed in the pharmaceutical composition at levels lower than that required in order to achieve the desired therapeutic effect and gradually increase the dosage until the desired effect is achieved.

In general, a suitable daily dose of a compound of the invention will be that amount of the compound which is the lowest dose effective to produce a therapeutic effect. Such an effective dose will generally depend upon the factors described above. Generally, intravenous and subcutaneous doses of the compounds of this invention for a patient will range from about 0.0001 to about 100 mg per kilogram of body weight per day, more preferably from about 0.01 to about 50 mg per kg per day, and still more preferably from about 1.0 to about 100 mg per kg per day.

If desired, the effective daily dose of the active compound may be administered as two, three, four, five, six or more sub-doses administered separately at appropriate intervals throughout the day, optionally, in unit dosage forms. Page 100-101.

31. However, applicant does not teach how to evaluate which tetracycline compounds have what effect on different diseases? Or how they modulate RNA splicing in different disease states? How would a skilled artisan decide between two different tetracycline derivatives?

32. Applicant's disclose hundreds of specific tetracycline compounds (pages 16-79), and teaches the disclosure of thousands of derivatives of those compounds, including all tautomers thereof (page 92). Do all tetracycline derivatives cause the exact same

down-regulation or up-regulation of genes as those taught by applicant in example 3 in diseases associated with splicing? Are they all modulated to the same extent? Would the modulation of RNA splicing in murine macrophages be the same in human liver cells? Are there disease states where the down-regulation of those genes disclosed by applicant in example 3 would actually exacerbate the disease state rather than "treat" and therefore actually be contraindicative to treat that particular DMTR associated with splicing?

33. Applicant fails to disclose the particular genes that are modulated in Example 3, table 3. What genes are these? Would the down regulation of these genes be detrimental in treating someone with parkinsonism disease but beneficial for treating someone with muscular dystrophy? Applicant does not teach any specifics, other than to suggest that the skilled artisan would know how to decipher between the hundreds of compounds disclosed in the specification.

34. The invention as claimed reads on a method of treating any subject, including animals, and humans, using any tetracycline compound for any disease state associated with spicing. There is no teaching in the specification of how to alter the method of treating a naked mole rat suffering from cystic fibrosis disease to treating a human suffering from colon cancer.

35. *4) State of the art*. The art shows that chemically modified tetracyclines are highly variable. Liu et al (The lipophilicity, Pharmacokinetics, and Cellular Uptake of Different Chemically-Modified Tetracyclines (CMTs). Current medicinal Chemistry, 2001. 8:243-252) teaches that CMTs have great therapeutic potential not as antibiotics,

but as therapeutic agents for disease states (see introduction, page 243), and that at least one CMT used in his study was currently being tested to treat humans (page 251, last paragraph). Liu studies 9 different CMTs (Figure 1). Liu teaches that different CMTs have different properties which effect cellular uptake, clearance, and half-life of the CMT. These differences can be seen between *in vivo* studies compared to *in vitro* studies of the same CMT (page 243-244). Liu further teaches that the time for different CMTs to reach their peak maximum serum levels (C_{max}) and half-lives varied significantly (Page 248-249, Figure 3 and Table 1). Liu suggest that these ranges may be the result of poor absorption from the gastrointestinal tract, instability in the blood, rapid elimination from the serum (from urinary uptake, rapid detoxification or rapid tissue uptake), and that different organs showed different levels of uptake of the different CMTs (see page 249-250 and table 1). Liu further teaches that one CMT (CMT-7) tested was both unstable both in vitro and in vivo (page 250) and that the molecule was difficult to study because it is a tautomer and fluctuates between several forms (page 251). Liu stresses, "to asses the therapeutic potential of this series of compounds, their in vitro efficacy described above has to be "matched" to the pharmacokinetics, safety, and efficacy profile in vivo."

36. Hertweck et al (inhibition of nuclear pre-mRNA splicing by antibiotics in vitro. European Journal of Biochemistry, 2002. 269:175-183) teaches that a tetracycline derivative is capable of inhibiting splicing of nuclear pre-mRNA (see abstract). How would the skilled artisan know which tetracycline derivative is appropriate for which DTMR associated with splicing? Would it be improper to use a tetracycline derivate in a

DTMR-associated with splicing, when the disease is caused by aberrant splicing, or would the inhibition of splicing lead to other diseases? What DTMR associated with diseases need to be treated by inhibiting splicing? What other tetracycline derivatives inhibit splicing?

37. Chakkalakal et al (Molecular, cellular and pharmacological therapies for Duchenne/Becker muscular dystrophies. The FASEB Journal, 2005. 19(8):880-91) teaches that because some mutations known to cause DMD are due to the formation of a premature stop codon, one group studied using the antibiotic gentamicin to cause suppression of stop codons, and there was some degree of restoration of muscle fibers. However, Chakkalakal that reports a second group trying to repeat the experiments were unsuccessful (see page 886, column I).

38. *5) Unpredictability of the art.* The art is highly unpredictable. The use of modified tetracycline compounds for uses other than antibiotics is growing, but the art reveals how these compounds react differently between in vitro and in vivo settings, as well as tissue-to-tissue variability, and have high degrees of variability in serum levels and half-lifes. The art teaches that this variability is due to the structure of the tetracycline compound, but also to unknown *in vivo* environments which effect the tetracycline compound. The art also shows that antibiotic treatment for muscular dystrophy is not a reproducible or reliable alternative. Applicants have not taught one of skill in the art how to decipher which of the thousands of tetracycline derivatives in the instant specification would be able to overcome known obstacles in the art. Applicant's have not shown any in vivo data to investigate the cellular uptake, half-life, clearance, etc. of the thousands

of compounds disclosed, not how to address these issues, other than altering the effective amount based on compound, and size and weight of the subject. A skilled artisan would therefore be required to determine how each of the thousands of tetracycline compounds react *in vivo* in order to determine which one to even begin testing for a particular DTMR. Applicants have not disclosed how to treat individual DTMRs associated with splicing, either in vitro nor in vivo. Applicants have not addressed the differences associated with treating a DTMR non associated with splicing from one that is associated with splicing. The skilled artisan would therefore be forced to conduct undue trial and error in order to practice the claimed invention, depending on which DMTR, which subject, and which tetracycline compound derivative was being utilized for treating the subject.

39. *6) Level of skill in the art.* The level of skill is high. The invention as claimed reads on a method of treating any subject, including animals, and humans. There is no teaching on how to adjust the method between different subjects. There is no teaching of how to decipher which tetracycline compounds are to be used for specific DMTRs associated with splicing, but not to be used for other DMTRs (with or without splicing). Applicant's disclose thousands of tetracycline compounds, but only show 1 single example of RNA modulation in two murine macrophage cell lines after exposure to two tetracycline compounds. Applicants do not disclose what genes are actually altered, nor if that alteration results in a modulation of proteins. Applicants teach that the only factors needed to determine "effective amount" is size and weight of the subject, and the choice of tetracycline compound, but does not teach how one of skill in the art would

choose one derivative disclosed over another out of the thousands disclosed in the specification. Applicant does not address known obstacles in the art regarding the administration of different tetracycline compounds. The skilled artisan would therefore be forced to conduct undue trial and error in order to practice the claimed invention, depending on which DMTR associated with splicing, which subject, and which tetracycline compound derivative was being utilized for treating the subject.

40. *7) The breadth of the claims.* The breadth of the claims are broad. The invention as claimed reads on a method of treating any subject, including animals, and humans, using any tetracycline compound for any disease state associated with a DTMR associated with splicing.

41. Given the above analysis of the factors which the courts have determined are critical in ascertaining whether a claimed invention is enabled, including the highly unpredictable art, the scarcity of working examples provided by applicant, the lack of guidance by the applicant, and the broad nature of the invention it must be considered that the skilled artisan would have to conduct undue and excessive experimentation in order to practice the claimed invention.

Response to Arguments

42. Applicant's arguments filed 11/05/07 have been fully considered but they are not persuasive. Applicants traverse the 102 1st enablement rejection of claims 1-6, 8,10,11,36-37,54,and 57. Applicants argue that the specification is enabling with “the general synthetic methods described in the specification and the examples, which describe the synthesis or examples of the compound. That pages 6-7 disclose assays

for measuring splicing and spliced forms or mRNA, and references which provide guidance for measuring splicing, and that there are several DTMS associated with splicing discloses on page 9, that one skilled in the art in possession of the specification at the time it was filed would have been able to practice the invention with no more than routine experimentation, and that just because the experimentation is complex does not make it undue. And that if one skilled in the art based on knowledge of compounds having similar physiological or biological activity, would be able to discern an appropriate dosage or method without use of undue experimentation, this would satisfy 35 USC 112 1st paragraph.

43. The examiner is respectfully not persuaded. The examiner agrees that it is through the culmination of Wands factors which determines whether undue experimentsion is necessary in light of the specification. However, in light of the analysis above, the examiner maintains that the art shows that treatment with tetracycline derivatives as therapeutics other then antibiotics is not routine, as evidenced by Liu et al (see above), that diseases such as muscular dystrophy that have been treated with antibiotics have had irreproducible results as evidenced by Chakkalakal (see above) and Hertweck teaches that tetracycline derivatives are capable of inhibiting splicing, which taken together suggest that the single administration of tetracycline derivatives to treat any DTMR associated with splicing is not routine. Taking the state of the art, the unpredictability of the state of the art in regard to specific DTMR associated with splicing listed in the claims, added to the fact that applicant's disclose thousands of possible tetracycline derivatives, and argue that

any one of them can be used to treat any single DTMR associated with splicing, but in fact do not disclose a single working example of treating a DTMR associated with splicing, and as applicant's themselves admit, the teachings of the specification are "generic" and thus not specific for treating a DTMR associated with splicing, the examiner maintains that the skilled artisan would be forced to perform undue experimentation in order to make and use the claimed invention. Applicant's arguments that the specification provides assays for measuring RNA splicing are irrelevant, as the specification does not disclose how splicing is supposed to be modulated for any DTMR associated with splicing. Thus the skilled artisan would not be able to recognize if a change of splicing was a "treatment" as there is no disclosure of successful splicing modulation, or any teaching of what it ought be in different disease states. ***Thus this rejection is maintained.***

44. Claims 1, 36-47, 54, 57-64 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. ***This rejection is modified to address amendments to claims.***

45. Applicants claim a method of treating any subject for any Disorder treatable by Modulation of RNA (DMTR) associated with splicing comprising the administration to the subject an effective amount of any tetracycline compound wherein the DTMR

associated with splicing is treated. The method is further limited wherein the modulation of splicing of the RNA increases or decreases RNA (via crytptic splice sites, ESEs or ISEs, ESSs or ISSes etc) and the subject is an animal. The method is further limited wherein the tetracycline compound is a compound comprising thousands of a different tetracycline molecules comprising different side chains groups, and the DMTR associated with splicing is cystic fibrosis, muscular dystrophy, eosinophilic diseases frontotemporal dementia with parkinsonism, a neurodegenerative disorder or β-thalassemia.

46. Thus the invention encompasses a treatment for any DMTR associated with spelcing, on any subject using any tetracycline compound.

47. DMTRs associated with splicing are not specifically defined. The instant specification teaches:

48. Other exemplary DTMRs include disorders caused by, or associated with splicing. For example, some disorders associated with defects in pre-mRNA processing result from a loss of function due to mutations in regulatory elements of a gene. Examples of such mutations are described in Krawczak et al. (1992) Hum. Genet, 90:41- 54; and Nakai et al. (1994) Gene 14:171-177. Other DTMR include disorders which have been attributed to a change in trans-acting factors. Examples of DTMRs which are associated with splicing include those described in Philips et al. (2000), Cell. Mol. Life Sci., 57:235-249), as well as, FTDP- 17 (frontotemporal dementia with parkinsonism) and/β-thalassemia.

49. Certain DTMRs associated with splicing include those which are generated by point mutations that either destroy splice-sites or generate new cryptic sites in the vicinity of normally used exons. Examples of such DTMRs include cystic fibrosis (Friedman et al. (1999) Jr. Biol. Chem. 274:36193-36199), muscular dystrophy (Wilton et al. (1999) Neuromuscul. Disord. 9:330-338), and eosinophilic diseases (Karras et al., (2000) Mol. Pharamcol. 58:380-387).

50. Other DTMRs include cancers which may change splicing patterns during cancer formation and progression. Example of such cancers include, but are not limited to leukemia, colon/rectal cancer, myeloid leukemia, breast cancer; gastric carcinomas, acute leukemia, multiple myeloma, myeloid cell leukemia, lung cancer, prostate cancer,

etc. Addition DTMRs associated with splicing are discussed in Stoss et al., (2000), Gene Ther. Mol. Biol. 5:9-30). (page 9, lines 8-29).

51. This "definition" is virtually open-ended, and reads on thousands of conditions and disease states.

52. The claims therefore read on a genus of methods of any in vivo or in vitro treatment of any DMTR associated with splicing in any subject using any tetracycline compound.

53. The written description requirement for a genus may be satisfied by sufficient description of a representative number of species by actual reduction to practice or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show that applicant was in possession of the claimed invention.

54. In the instant case, applicants provide ample examples of making different tetracycline compounds (see examples 1-2), but do not, in fact, provide any data providing evidence for the in vivo treatment of any DMTR associated with splicing using any of these tetracycline compounds. Applicants do not provide explicit instructions on how to differentiate between the advantages of using one tetracycline compound over another, nor in what condition a particular tetracycline compound would be appropriate for, and which DTMR associated with splicing conditions that that particular compound would be indicative or contraindicative for. Applicants instructions including altering the "effective amount" based on size and weight of the subject, and the compound used,

but offer no details on how to determine what factors of size, weight, and more importantly, what compounds are to be considered for effective amount. The lone reference in vitro "treatment" of 2 murine macrophage cell lines, only demonstrates that there is an alteration of RNA as a result of the administration of 2 different tetracycline compounds. It does not disclose what DMTR that is supposed to be representative for, nor what genes are up-regulated or down-regulated. It does not disclose if those alterations resulted in protein modulation. Applicants do not disclose how, if the treatments utilized every tetracycline compound within the scope of the claims, how one would overcome known obstacle in the art of modified tetracyclines (see above).

55. The skilled artisan would be unable to describe, or envision, any specific method for treating any specific DMTR in any subject using any tetracycline compound disclosed in the claims. The skilled artisan would therefore conclude that the applicants have not provided any examples of treating any specific DMTR in any subject using any tetracycline compound in vitro or in vivo in light of the instant specification and claims. The skilled artisan would conclude that applicant's were not in possession of the claimed invention.

Response to Arguments

56. Applicant's arguments filed 11/05/07 have been fully considered but they are not persuasive. Applicants traverse the 112 1st written description rejection of claims 1-6, 8,10,11,36-37,54,and 57. Applicants argue that the specification properly describes the claims as amended. Applicants argue that the specification discloses assays for measuring splicing and spliced forms of mRNA, and references which provide guidance

for measuring splicing, and that there are several DMTRs associated with splicing are disclosed on page 9. Applicants argue that page 80-86 and example 1 "provided synthetic methods for the synthesis of representative substituted tetracycline compounds of the invention for use in treating a DMTR associated with splicing.

57. The examiner is respectfully not persuaded. The examiner reminds applicant's that the instant claims are drawn to a *method of treating using the tetracycline compounds*, which read on treating an animal, including humans, not the composition of the tetracycline compounds, nor methods of making the tetracycline compounds. Thus the written description requirement must be commensurate with the scope of the claimed genus. While the instant specification does teach making a number of tetracycline compounds, the specification does not present a representable number of *methods for treating a DTMR associated with splicing*. There is no teaching of what tetracycline compounds should be, or should not be used to treat any DTMR associated with splicing particularly, and rather teaches that any tetracycline compound can be used to treat any DTMR. The instant working examples do not specifically "treat" any DTMR associated with splicing, and the generic methods pointed by applicant, regarding assays for measuring RNA splicing are irrelevant, as the specification does not disclose how splicing is supposed to be modulated for any DTMR associated with splicing. ***Thus this rejection is maintained.***

58. It is noted that this Office Action contains rejections of the same claims under 35 USC 112, 1st (enablement and written description) and 35 USC 102 (b/e). While these

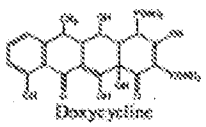
rejections may seem contradictory, they are not because each is based upon a different legal analysis, i.e. sufficiency of the disclosure of the instant application to support claims under 35 USC 112, 1st paragraph vs. sufficiency of a prior art disclosure to anticipate or render obvious an embodiment(s) of the claimed invention (See *In re Hafner*, 161 USPQ 783 (CCPA 1969)).

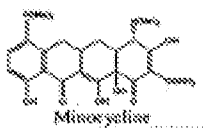
For purposes of prosecution, the following is defined:

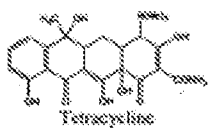
59. The specification teaches:

> In an embodiment, when the DTMR is an aortic aneurysm, the tetracycline Compound is not doxycycline. In another embodiment, when the DTMR is Huntington's disease, the tetracycline compound is not minocycline. In another embodiment, when the DTMR is cerebral ischemia, the tetracycline compound is not tetracycline. In other embodiments, when the DTMR is asthma, the tetracycline compound is not minocycline or doxycycline. Page 10.

The instant specification teaches the structures of substituted tetracycline compounds doxycycline, minocycline, as well as tetracycline:







Pruss et al (Inducible nitric oxide synthase does not mediate brain damage after transient focal cerebral ischemia in mice. Journal of Cerebral Blood Flow and Metabolism, 2007) teaches that cerebral ischemia results in differential splicing of iNOS mRNA.

Thus using the broadest reasonable interpretation, cerebral ischemia reads on "A DTMR associated with splicing."

Fonager et al (Transcription and alternative splicing in the yir multigene family of the malaria parasite *Plasmodium y. yoelii*: identification of motifs suggesting epigenetic and post-transcriptional control of RNA expression. Molecular Biochemical Parasitology, 2007, 156(1):1-11) teaches that the pathogen responsible for malaria functions through differential splicing of certain genes. Fonager states, "Together these data suggest that different *pir* genes may be active at different stages of the life cycle of *P. yoelii* and may have different functions" (see abstract).

Thus using the broadest reasonable interpretation, malaria reads on "A DTMR associated with splicing."

Claim Rejections - 35 USC § 102

60. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

61. Claims 1, 37-38, 58, 60-62 are rejected under 35 U.S.C. 102(b) as being taught by Yrjanheikki et al (Tetracyclines Inhibit Microglial Activation and are Neuroprotective in Global Brain Ischemia. PNAS, 1998. 95:15769-15574) (of record 05/04/07). Claims 1, 37-38 recite a method for treating a subject for a DTMR associated with splicing comprising administering an effective amount of a tetracycline compound, such that the DTMR associated with splicing is treated, wherein said effective amount is effective to modulate splicing of RNA by decreasing splicing or mRNA, wherein the subject is an animal. The method is further limited wherein the tetracycline compound is a substituted compound comprising formula (I). ***This rejection is modified to address amendments to claims.***

62. DTMRs associated with splicing are not specifically defined. The instant specification teaches:

63. Other exemplary DTMRs include disorders caused by, or associated with splicing. For example, some disorders associated with defects in pre-mRNA processing result from a loss of function due to mutations in regulatory elements of a gene. Examples of such mutations are described in Krawczak et al. (1992) Hum. Genet, 90:41- 54; and Nakai et al. (1994) Gene 14:171-177. Other DTMR include disorders which have been attributed to a change in trans-acting factors. Examples of DTMRs which are associated with splicing include those described in Philips et al. (2000), Cell. Mol. Life Sci., 57:235-249), as well as, FTDP- 17 (frontotemporal dementia with parkinsonism) and/β-thalassemia.

64. Certain DTMRs associated with splicing include those which are generated by point mutations that either destroy splice-sites or generate new cryptic sites in the vicinity of normally used exons. Examples of such DTMRs include cystic fibrosis (Friedman et al. (1999) Jr. Biol. Chem. 274:36193-36199), muscular dystrophy (Wilton

et al. (1999) Neuromuscul. Disord. 9:330-338), and eosinophilic diseases (Karras et al., (2000) Mol. Pharamcol. 58:380-387).
65. Other DTMRs include cancers which may change splicing patterns during cancer formation and progression. Example of such cancers include, but are not limited to leukemia, colon/rectal cancer, myeloid leukemia, breast cancer; gastric carcinomas, acute leukemia, multiple myeloma, myeloid cell leukemia, lung cancer, prostate cancer, etc. Addition DTMRs associated with splicing are discussed in Stoss et al., (2000), Gene Ther. Mol. Biol. 5:9-30). (page 9, lines 8-29).

66. Yrjanheikki teaches the administration of the substituted tetracycline compounds doxycycline, minocycline, as well as tetracycline, prior to, and 30 minutes after, ischemia (see abstract, and Drug Treatment section page 15770). Cerebral ischemia reads on a "DTMR asscoaited with Splicing" as evidenced by Pruss et al (above). Yrjankeikki teaches that doxycycline and minocycline, but not tetracycline are neuroprotective, and minocycline inhibits induction of interleukin-1β-converting enzyme mRNA, decreases induction of iNOS mRNA, and prevents NOS protein expression (see page 15769, second column, 2nd full paragraph.) Yrjanheikki uses an *in vivo* model of a gerbil model of forebrain ischemia (see page15769-15770). Thus Yrjanheikki teaches the claimed invention.

Response to Arguments

67. Applicant's arguments filed 11/05/07 have been fully considered but they are not fully persuasive. Applicant's traverse the rejection of claims 1, 2, 8, 10, 11, 36-38. Applicants argue that Yrjanheikki does not read on a DTMR associated with splicing, but the use of a tetracycline as a protective agent against ischemic stroke. The examiner does not agree. Cerebral ischemia inherently reads on a DTMR associated with splicing, as cerebral ischemia causes differential splicing of iNOS (see Pruss et al). Additionally, in the teaching of Yrjanheikki there is no provision of when the tetracycline

is administered, and can be administered as a preventative or as a treatment. Yrjanheikki administers the tetracycline both prior to and 30 minutes after injury (see abstract) and sees a reduction of iNOS RNA and protein as a result of administration. Thus this rejection is maintained.

68. Claims 1, 37-47, 62 are rejected under 35 U.S.C. 102(e) as being anticipated by Nelson et al (US Patent No. 6,500,812) listed in applicant's IDS form dated 06/08/06. Claims 1, 37-47, 62 recite a method of treating a DTMR comprising administering to said subject an effective amount of a tetracycline compound, such that said DTMR is treated, wherein the subject is an animal, and using a variety of substituted tetracycline compounds. This method reads on treating bacterial, fungal, and general disease states (see specification page 8-10). ***This rejection is modified to address amendments to claims.***

69. Nelson et al (US Patent No. 6,500,812) teaches a method of treating a tetracycline response state in a mammal, comprising the administration of a tetracycline compound, such that the tetracycline state (including cancer) is treated (see abstract and claims).

The applied reference has a common assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in

the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Response to Arguments

70. Applicant's arguments filed 11/05/07 have been fully considered but they are not fully persuasive. Applicant's traverse the rejection of claims 1, 2, 8, 10, 11, 36-38. Applicants argue that Nelson (US Patent No. 6,500,812) does not read on a DTMR associated with splicing. The examiner does not agree. Cancer inherently reads on a DTMR associated with splicing, as the instant specification teaches that cancers are a DTMR associated with splicing (see page 9, lines 8-29). Thus this rejection is maintained.

71. Additionally, while applicant has provided a statement saying that the referenced US Patent was commonly owned at the time of the instant invention, applicant has not provided information stating that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131. As such, the reference continues to constitute prior art.

72. Claims 1, 37-47, 62 are rejected under 35 U.S.C. 102(e) as being anticipated by Nelson et al (US Patent No. 6,624,168) listed in applicant's IDS form dated 06/08/06. Claims 1, 37-47, 62 recite a method of treating a DTMR comprising administering to said subject an effective amount of a tetracycline compound, such that said DTMR is treated, wherein the subject is an animal, and using a variety of substituted tetracycline

compounds. This method reads on treating bacterial, fungal, and general disease states (see specification page 8-10). ***This rejection is modified to address amendments to claims.***

73. Nelson et al (US Patent No. 6,624,168) teaches a method of treating a tetracycline response state in a mammal, comprising the administration of a tetracycline compound, such that the tetracycline state (including cancer) is treated (see abstract and claims).

The applied reference has a common assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Response to Arguments

74. Applicant's arguments filed 11/05/07 have been fully considered but they are not fully persuasive. Applicant's traverse the rejection of claims 1, 2, 8, 10, 11, 36-38. Applicants argue that Nelson (US Patent No. 6,624,168) does not read on a DTMR associated with splicing. The examiner does not agree. Cancer inherently reads on a DTMR associated with splicing, as the instant specification teaches that cancers are a DTMR associated with splicing (see page 9, lines 8-29). Thus this rejection is maintained.

75. Additionally, while applicant has provided a statement saying that the referenced US Patent was commonly owned at the time of the instant invention, applicant has not provided information stating that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131. As such, the reference continues to constitute prior art.

76. Claims 1, 37-47, 62 are rejected under 35 U.S.C. 102(e) as being anticipated by Nelson et al (US Patent No. 6,642,270) listed in applicant's IDS form dated 06/08/06. Claims 1, 37-47, 62 recite a method of treating a DTMR comprising administering to said subject an effective amount of a tetracycline compound, such that said DTMR is treated, wherein the subject is an animal, and using a variety of substituted tetracycline compounds. This method reads on treating bacterial, fungal, and general disease states (see specification page 8-10). ***This rejection is modified to address amendments to claims.***

77. Nelson et al (US Patent No. 6,642,270) teaches a method of treating a tetracycline response state in a mammal, comprising the administration of a tetracycline compound, such that the tetracycline state (including cancer) is treated (see abstract and claims).

The applied reference has a common assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome

either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Response to Arguments

78. Applicant's arguments filed 11/05/07 have been fully considered but they are not fully persuasive. Applicant's traverse the rejection of claims 1, 2, 8, 10, 11, 36-38. Applicants argue that Nelson (US Patent No. 6,642,270) does not read on a DTMR associated with splicing. The examiner does not agree. Cancer inherently reads on a DTMR associated with splicing, as the instant specification teaches that cancers are a DTMR associated with splicing (see page 9, lines 8-29). Thus this rejection is maintained.

79. Additionally, while applicant has provided a statement saying that the referenced US Patent was commonly owned at the time of the instant invention, applicant has not provided information stating that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131. As such, the reference continues to constitute prior art.

80. Claims 1, 37-47, 62 are rejected under 35 U.S.C. 102(e) as being anticipated by Nelson et al (US Patent No. 6,683,068) listed in applicant's IDS form dated 06/08/06. Claims 1, 37-47, 62 recite a method of treating a DTMR comprising administering to said subject an effective amount of a tetracycline compound, such that said DTMR is

treated, wherein the subject is an animal, and using a variety of substituted tetracycline compounds. This method reads on treating bacterial, fungal, and general disease states (see specification page 8-10). ***This rejection is modified to address amendments to claims.***

81. Nelson et al (US Patent No. 6,683,068) teaches a method of treating a DTMR including cancers in a human, comprising the administration of a tetracycline compound, such that the DTMR is treated (see abstract, column 24, lines 7-11 and claims).

The applied reference has a common assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Response to Arguments

82. Applicant's arguments filed 11/05/07 have been fully considered but they are not fully persuasive. Applicant's traverse the rejection of claims 1, 2, 8, 10, 11, 36-38. Applicants argue that Nelson (US Patent No. 6,683,068) does not read on a DTMR associated with splicing. The examiner does not agree. Cancer inherently reads on a DTMR associated with splicing, as the instant specification teaches that cancers are a DTMR associated with splicing (see page 9, lines 8-29). Thus this rejection is maintained.

83. Additionally, while applicant has provided a statement saying that the referenced US Patent was commonly owned at the time of the instant invention, applicant has not provided information stating that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131. As such, the reference continues to constitute prior art.

84. Claims 1, 37-47, 62 are rejected under 35 U.S.C. 102(e) as being anticipated by Nelson et al (US Patent No. 6,818,634) listed in applicant's IDS form dated 06/08/06. Claims 1, 37-47, 62 recite a method of treating a DTMR comprising administering to said subject an effective amount of a tetracycline compound, such that said DTMR is treated, wherein the subject is an animal, and using a variety of substituted tetracycline compounds. This method reads on treating bacterial, fungal, and general disease states (see specification page 8-10). ***This rejection is modified to address amendments to claims.***

85. Nelson et al (US Patent No. 6,818,634) teaches a method of treating a tetracycline response state in a mammal, comprising the administration of a tetracycline compound, such that the tetracycline state (including cancer) is treated (see abstract, column 26, lines 47-53 and claims).

The applied reference has a common assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome

either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Response to Arguments

86. Applicant's arguments filed 11/05/07 have been fully considered but they are not fully persuasive. Applicant's traverse the rejection of claims 1, 2, 8, 10, 11, 36-38. Applicants argue that Nelson (US Patent No. 6,818,634) does not read on a DTMR associated with splicing. The examiner does not agree. Cancer inherently reads on a DTMR associated with splicing, as the instant specification teaches that cancers are a DTMR associated with splicing (see page 9, lines 8-29). Thus this rejection is maintained.

87. Additionally, while applicant has provided a statement saying that the referenced US Patent was commonly owned at the time of the instant invention, applicant has not provided information stating that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131. As such, the reference continues to constitute prior art.

88. Claims 1, 37-47, 62 are rejected under 35 U.S.C. 102(e) as being anticipated by Nelson et al (US Patent No. 6,818,635) listed in applicant's IDS form dated 06/08/06. Claims 1, 37-47, 62 recite a method of treating a DTMR associated with splicing comprising administering to said subject an effective amount of a tetracycline

compound, such that said DTMR is treated, wherein the subject is an animal, and using a variety of substituted tetracycline compounds. This method reads on treating bacterial, fungal, and general disease states (see specification page 8-10). ***This rejection is modified to address amendments to claims.***

89. Nelson et al (US Patent No. 6,818,635) teaches a method of treating a DTMR (including cancer) in a human, comprising the administration of a tetracycline compound, such that the DTMR is treated (see abstract, column 42, lines 59-65) and claims).

The applied reference has a common assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Response to Arguments

90. Applicant's arguments filed 11/05/07 have been fully considered but they are not fully persuasive. Applicant's traverse the rejection of claims 1, 2, 8, 10, 11, 36-38. Applicants argue that Nelson (US Patent No. 6,818,635) does not read on a DTMR associated with splicing. The examiner does not agree. Cancer inherently reads on a DTMR associated with splicing, as the instant specification teaches that cancers are a DTMR associated with splicing (see page 9, lines 8-29). Thus this rejection is maintained.

91. Additionally, while applicant has provided a statement saying that the referenced US Patent was commonly owned at the time of the instant invention, applicant has not provided information stating that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131. As such, the reference continues to constitute prior art.

92. Claims 1, 37-47, 62 are rejected under 35 U.S.C. 102(e) as being anticipated by Nelson et al (US Patent No. 6,846,939) listed in applicant's IDS form dated 06/08/06. Claims 1, 37-47, 62 recite a method of treating a DTMR comprising administering to said subject an effective amount of a tetracycline compound, such that said DTMR is treated, wherein the subject is an animal, and using a variety of substituted tetracycline compounds. This method reads on treating bacterial, fungal, and general disease states (see specification page 8-10). ***This rejection is modified to address amendments to claims.***

93. Nelson et al (US Patent No. 6,846,939) teaches a method of treating a DTMR including cancer in a subject, comprising the administration of a tetracycline compound, such that the bacterial infection is treated (see abstract, column 25, lines 27-32 and claims).

The applied reference has a common assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome

either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Response to Arguments

94. Applicant's arguments filed 11/05/07 have been fully considered but they are not fully persuasive. Applicant's traverse the rejection of claims 1, 2, 8, 10, 11, 36-38. Applicants argue that Nelson (US Patent No. 6,846,939) does not read on a DTMR associated with splicing. The examiner does not agree. Cancer inherently reads on a DTMR associated with splicing, as the instant specification teaches that cancers are a DTMR associated with splicing (see page 9, lines 8-29). Thus this rejection is maintained.

95. Additionally, while applicant has provided a statement saying that the referenced US Patent was commonly owned at the time of the instant invention, applicant has not provided information stating that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131. As such, the reference continues to constitute prior art.

96. Claims 1, 37-47, 62 are rejected under 35 U.S.C. 102(e) as being anticipated by Nelson et al (US Patent No. 6,849,615) listed in applicant's IDS form dated 06/08/06. Claims 1, 37-47, 62 recite a method of treating a DTMR associated with splicing comprising administering to said subject an effective amount of a tetracycline

compound, such that said DTMR is treated, wherein the subject is an animal, and using a variety of substituted tetracycline compounds. This method reads on treating bacterial, fungal, and general disease states (see specification page 8-10). ***This rejection is modified to address amendments to claims.***

97. Nelson et al (US Patent No. 6,849,615) teaches a method of treating a tetracycline response state in a mammal, comprising the administration of a tetracycline compound, such that the tetracycline state (including cancer) is treated (see abstract, column 16 lines 1-6 and claims).

The applied reference has a common assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Response to Arguments

98. Applicant's arguments filed 11/05/07 have been fully considered but they are not fully persuasive. Applicant's traverse the rejection of claims 1, 2, 8, 10, 11, 36-38. Applicants argue that Nelson (US Patent No. 6,849,615) does not read on a DTMR associated with splicing. The examiner does not agree. Cancer inherently reads on a DTMR associated with splicing, as the instant specification teaches that cancers are a DTMR associated with splicing (see page 9, lines 8-29). Thus this rejection is maintained.

99. Additionally, while applicant has provided a statement saying that the referenced US Patent was commonly owned at the time of the instant invention, applicant has not provided information stating that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131. As such, the reference continues to constitute prior art.

100. Claims 1, 37-47, 62 are rejected under 35 U.S.C. 102(e) as being anticipated by Draper et al (US Patent No. 7,045,507) listed in applicant's IDS form dated 06/08/06. Claims 1, 37-47, 62 recite a method of treating a DTMR associated with splicing comprising administering to said subject an effective amount of a tetracycline compound, such that said DTMR is treated, wherein the subject is an animal, and using a variety of substituted tetracycline compounds. This method reads on treating bacterial, fungal, and general disease states (see specification page 8-10). ***This rejection is modified to address amendments to claims.***

101. Draper et al (US Patent No. 7,045,507) teaches a method of treating a DTMR including cancer, comprising the administration of a tetracycline compound, such that the DTMR is treated (see abstract, column 56 lines 1-5 and claims).

The applied reference has a common assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in

the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Response to Arguments

102. Applicant's arguments filed 11/05/07 have been fully considered but they are not fully persuasive. Applicant's traverse the rejection of claims 1, 2, 8, 10, 11, 36-38. Applicants argue that Draper et al (US Patent No. 7,045,507) does not read on a DTMR associated with splicing. The examiner does not agree. Cancer inherently reads on a DTMR associated with splicing, as the instant specification teaches that cancers are a DTMR associated with splicing (see page 9, lines 8-29). Thus this rejection is maintained.

103. Additionally, while applicant has provided a statement saying that the referenced US Patent was commonly owned at the time of the instant invention, applicant has not provided information stating that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131. As such, the reference continues to constitute prior art.

104. Claims 1, 37-47, 62 are rejected under 35 U.S.C. 102(e) as being anticipated by Nelson et al (US Patent No. 7,094,806) listed in applicant's IDS form dated 06/08/06. Claims 1, 37-47, 62 recite a method of treating a DTMR associated with splicing comprising administering to said subject an effective amount of a tetracycline compound, such that said DTMR is treated, wherein the subject is an animal, and using

a variety of substituted tetracycline compounds. This method reads on treating bacterial, fungal, and general disease states (see specification page 8-10). ***This rejection is modified to address amendments to claims.***

105. Nelson et al (US Patent No. 7,094,806) teaches a method of treating a tetracycline response state in a mammal, comprising the administration of a tetracycline compound, such that the tetracycline state (including cancer) is treated (see abstract, column 12 lines 36-41 and claims).

The applied reference has a common assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Response to Arguments

106. Applicant's arguments filed 11/05/07 have been fully considered but they are not fully persuasive. Applicant's traverse the rejection of claims 1, 2, 8, 10, 11, 36-38. Applicants argue that Nelson (US Patent No. 7,094,806) does not read on a DTMR associated with splicing. The examiner does not agree. Cancer inherently reads on a DTMR associated with splicing, as the instant specification teaches that cancers are a DTMR associated with splicing (see page 9, lines 8-29). Thus this rejection is maintained.

107. Additionally, while applicant has provided a statement saying that the referenced US Patent was commonly owned at the time of the instant invention, applicant has not provided information stating that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131. As such, the reference continues to constitute prior art.

108. Claims 1, 37-47, 62 are rejected under 35 U.S.C. 102(e) as being anticipated by Draper et al (US Patent Publication No. US 20040242548) listed in applicant's IDS form dated 06/08/06. Claims 1, 37-47, 62 recite a method of treating a DTMR associated with splicing comprising administering to said subject an effective amount of a tetracycline compound, such that said DTMR is treated, wherein the subject is an animal, and using a variety of substituted tetracycline compounds. This method reads on treating bacterial, fungal, and general disease states (see specification page 8-10).
109. Draper et al (US Patent Publication No. US 20040242548) teaches a method of treating malaria (A DTMR associated with splicing) in a subject, comprising the administration of a tetracycline compound, such that malaria is treated (see abstract and claims).

The applied reference has a common assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in

the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Response to Arguments

110. Applicant's arguments filed 11/05/07 have been fully considered but they are not fully persuasive. Applicant's traverse the rejection of claims 1, 2, 8, 10, 11, 36-38. Applicants argue that Draper et al (US Patent Publication No. US 20040242548) does not read on a DTMR associated with splicing. The examiner does not agree. Malaria inherently reads on a DTMR associated with splicing, as taught by Fonager et al (see above). Thus this rejection is maintained.

111. Additionally, while applicant has provided a statement saying that the referenced US Patent application was commonly owned at the time of the instant invention, applicant has not provided information stating that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131. As such, the reference continues to constitute prior art.

112. Claims 1, 37-47, 62 are rejected under 35 U.S.C. 102(e) as being anticipated by Huss et al (US Patent Publication No. US 20040266740) listed in applicant's IDS form dated 06/08/06. Claims 1, 37-47, 62 recite a method of treating a DTMR associated with splicing comprising administering to said subject an effective amount of a tetracycline compound, such that said DTMR associated with splicing is treated, wherein the subject is an animal, and using a variety of substituted tetracycline

compounds. This method reads on treating bacterial, fungal, and general disease states (see specification page 8-10). ***This rejection is modified to address amendments to claims.***

113. Huss et al (US Patent Publication No. US 20040266740) teaches a method of treating a tetracycline responsive state including cancers (paragraph 0075) in a human, comprising the administration of a tetracycline compound, such that the tetracycline state is treated (see abstract and claims).

The applied reference has a common assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Response to Arguments

114. Applicant's arguments filed 11/05/07 have been fully considered but they are not fully persuasive. Applicant's traverse the rejection of claims 1, 2, 8, 10, 11, 36-38. Applicants argue that Huss et al (US Patent Publication No. US 20040266740) does not read on a DTMR associated with splicing. The examiner does not agree. Cancer inherently reads on a DTMR associated with splicing, as the instant specification teaches that cancers are a DTMR associated with splicing (see page 9, lines 8-29). Thus this rejection is maintained.

115. Additionally, while applicant has provided a statement saying that the referenced US Patent application was commonly owned at the time of the instant invention, applicant has not provided information stating that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131. As such, the reference continues to constitute prior art.

116. Claims 1, 37-47, 62 are rejected under 35 U.S.C. 102(e) as being anticipated by Nelson et al (US Patent Publication No. US 20050026876) listed in applicant's IDS form dated 06/08/06. Claims 1, 37-47, 62 recite a method of treating a DTMR associated with splicing comprising administering to said subject an effective amount of a tetracycline compound, such that said DTMR is treated, wherein the subject is an animal, and using a variety of substituted tetracycline compounds. This method reads on treating bacterial, fungal, and general disease states (see specification page 8-10).

This rejection is modified to address amendments to claims.

117. Nelson et al (US Patent Publication No. US 20050026876) teaches a method of treating a tetracycline responsive state (including cancer see paragraph 0127) in a mammal, comprising the administration of a tetracycline compound, such that the tetracycline state is treated (see abstract and claims).

The applied reference has a common assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome

either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Response to Arguments

118. Applicant's arguments filed 11/05/07 have been fully considered but they are not fully persuasive. Applicant's traverse the rejection of claims 1, 2, 8, 10, 11, 36-38. Applicants argue that Nelson et al (US Patent Publication No. US 20050026876) does not read on a DTMR associated with splicing. The examiner does not agree. Cancer inherently reads on a DTMR associated with splicing, as the instant specification teaches that cancers are a DTMR associated with splicing (see page 9, lines 8-29). Thus this rejection is maintained.

119. Additionally, while applicant has provided a statement saying that the referenced US Patent application was commonly owned at the time of the instant invention, applicant has not provided information stating that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131. As such, the reference continues to constitute prior art.

120. Claims 1, 37-47, 62 are rejected under 35 U.S.C. 102(e) as being anticipated by Draper et al (US Patent Publication No. US 20050070510) listed in applicant's IDS form dated 06/08/06. Claims 1, 37-47, 62 recite a method of treating a DTMR associated with splicing comprising administering to said subject an effective amount of a

tetracycline compound, such that said DTMR is treated, wherein the subject is an animal, and using a variety of substituted tetracycline compounds. This method reads on treating bacterial, fungal, and general disease states (see specification page 8-10).

This rejection is modified to address amendments to claims.

121. Draper et al (US Patent Publication No. US 20050070510) teaches a method of treating a fungus and fungal infection including those in cancer patients, comprising the administration of a tetracycline compound, such that the fungal infection is treated (see abstract, paragraph 003 and claims).

The applied reference has a common assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Response to Arguments

122. Applicant's arguments filed 11/05/07 have been fully considered but they are not fully persuasive. Applicant's traverse the rejection of claims 1, 2, 8, 10, 11, 36-38. Applicants argue that Draper et al (US Patent Publication No. US 20050070510) does not read on a DTMR associated with splicing. The examiner does not agree. Cancer inherently reads on a DTMR associated with splicing, as the instant specification teaches that cancers are a DTMR associated with splicing (see page 9, lines 8-29). Thus this rejection is maintained.

123. Additionally, while applicant has provided a statement saying that the referenced US Patent application was commonly owned at the time of the instant invention, applicant has not provided information stating that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131. As such, the reference continues to constitute prior art.

Conclusion

124. No claims are allowed.

125. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly A. Makar, Ph.D. whose telephone number is 571-272-4139. The examiner can normally be reached on 8AM - 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D. can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Kam/02/08/08

/David Guzo/
Primary Examiner
Art Unit 1636